

USPAT2

NEWS	5	JAN 13	IPC 8 searching in IFIPAT, IFIUDB, and IFICDB
NEWS	6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
NEWS	7	JAN 17	Pre-1988 INPI data added to MARPAT
NEWS	8	JAN 17	IPC 8 in the WPI family of databases including WPIFV
NEWS	9	JAN 30	Saved answer limit increased
NEWS	10	JAN 31	Monthly current-awareness alert (SDI) frequency added to TULSA
NEWS	11	FEB 21	STN AnaVist, Version 1.1, lets you share your STN AnaVist visualization results
NEWS	12	FEB 22	Status of current WO (PCT) information on STN
NEWS	13	FEB 22	The IPC thesaurus added to additional patent databases on STN
NEWS	14	FEB 22	Updates in EPFULL; IPC 8 enhancements added
NEWS	15	FEB 27	New STN AnaVist pricing effective March 1, 2006
NEWS	16	FEB 28	MEDLINE/LMEDLINE reload improves functionality
NEWS	17	FEB 28	TOXCENTER reloaded with enhancements
NEWS	18	FEB 28	REGISTRY/ZREGISTRY enhanced with more experimental spectral property data
NEWS	19	MAR 01	INSPEC reloaded and enhanced
NEWS	20	MAR 03	Updates in PATDPA; addition of IPC 8 data without attributes
NEWS	21	MAR 08	X.25 communication option no longer available after June 2006
NEWS	22	MAR 22	EMBASE is now updated on a daily basis
NEWS	23	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS	24	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
NEWS	25	APR 04	STN AnaVist \$500 visualization usage credit offered
NEWS EXPRESS			FEBRUARY 15 CURRENT VERSION FOR WINDOWS IS V8.01a, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 DECEMBER 2005. V8.0 AND V8.01 USERS CAN OBTAIN THE UPGRADE TO V8.01a AT <a href="http://download.cas.org/express/v8.0-Discover/">http://download.cas.org/express/v8.0-Discover/</a>

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FILE 'HOME' ENTERED AT 13:03:33 ON 05 APR 2006

=> file req

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SINCE FILE ENTRY	TOTAL SESSION
0.42	0.42

FILE 'REGISTRY' ENTERED AT 13:04:29 ON 05 APR 2006  
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STRUCTURE FILE UPDATES: 4 APR 2006 HIGHEST RN 879269-14-4  
DICTIONARY FILE UPDATES: 4 APR 2006 HIGHEST RN 879269-14-4

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TSCA INFORMATION NOW CURRENT THROUGH January 6, 2006

Please note that search-term pricing does apply when conducting SmartSELECT searches.

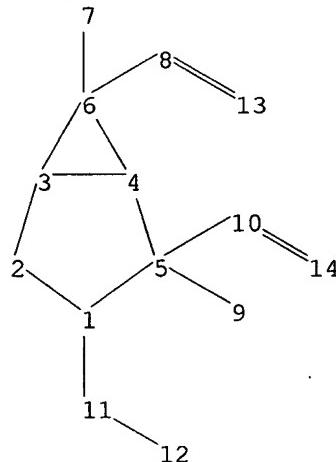
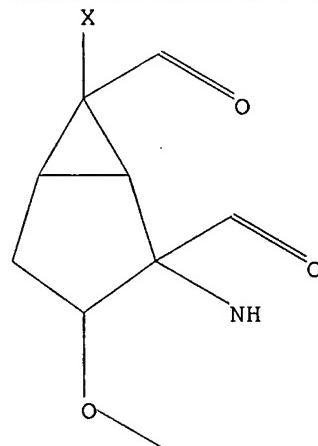
\*\*\*\*\*  
\*  
\* The CA roles and document type information have been removed from \*  
\* the IDE default display format and the ED field has been added, \*  
\* effective March 20, 2005. A new display format, IDERL, is now \*  
\* available and contains the CA role and document type information. \*  
\*  
\*\*\*\*\*

Structure search iteration limits have been increased. See HELP SLIMITS for details.

REGISTRY includes numerically searchable data for experimental and predicted properties as well as tags indicating availability of experimental property data in the original document. For information on property searching in REGISTRY, refer to:

<http://www.cas.org/ONLINE/UG/regprops.html>

=>  
Uploading C:\Documents and Settings\PZucker\My Documents\Examination Auxillary files\10500101\10500101 clm 2 core obv.str

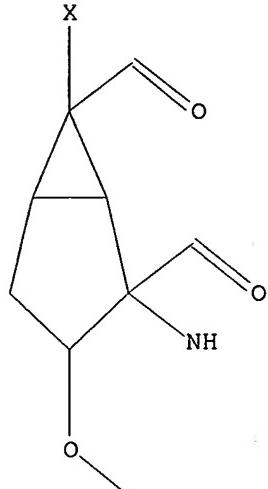


chain nodes :  
7 8 9 10 11 12 13 14  
ring nodes :  
1 2 3 4 5 6  
chain bonds :  
1-11 5-9 5-10 6-7 6-8 8-13 10-14 11-12  
ring bonds :  
1-2 1-5 2-3 3-4 3-6 4-5 4-6  
exact/norm bonds :  
1-2 1-5 1-11 2-3 3-4 3-6 4-5 4-6 5-9 8-13 10-14 11-12  
exact bonds :  
5-10 6-7 6-8

Match level :  
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS  
11:CLASS 12:CLASS 13:CLASS 14:CLASS

L1 STRUCTURE UPLOADED

=> d 11  
L1 HAS NO ANSWERS  
L1 STR



Structure attributes must be viewed using STN Express query preparation.

=> search 11 sss sam  
SAMPLE SEARCH INITIATED 13:04:55 FILE 'REGISTRY'  
SAMPLE SCREEN SEARCH COMPLETED - 11 TO ITERATE

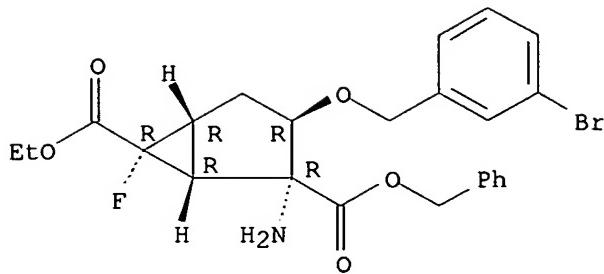
100.0% PROCESSED 11 ITERATIONS 9 ANSWERS  
SEARCH TIME: 00.00.01  
FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*  
BATCH \*\*COMPLETE\*\*  
PROJECTED ITERATIONS: 22 TO 418  
PROJECTED ANSWERS: 9 TO 360

L2 9 SEA SSS SAM L1

=> d scan

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[(3-bromophenyl)methoxy]-6-fluoro-, 6-ethyl 2-(phenylmethyl) ester, (1R,2R,3R,5R,6R)- (9CI)  
MF C24 H25 Br F N O5  
CI COM

Absolute stereochemistry.

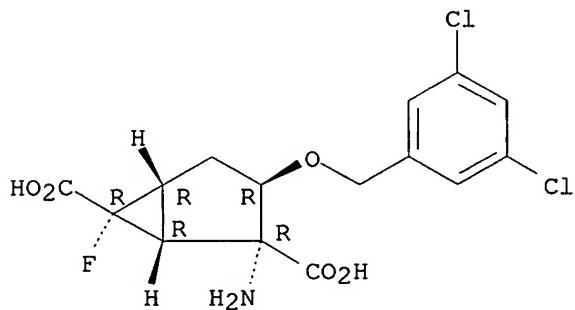


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):3

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[3,5-dichlorophenyl]methoxy]-6-fluoro-, (1R,2R,3R,5R,6R)- (9CI)  
 MF C15 H14 Cl2 F N O5

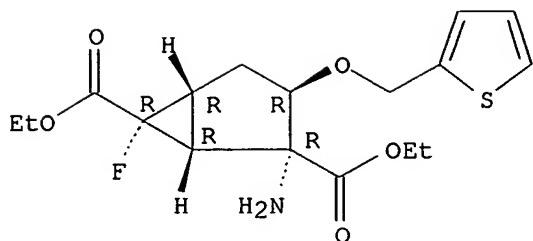
Absolute stereochemistry. Rotation (-).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-6-fluoro-3-(2-thienylmethoxy)-, diethyl ester, (1R,2R,3R,5R,6R)- (9CI)  
 MF C17 H22 F N O5 S  
 CI COM

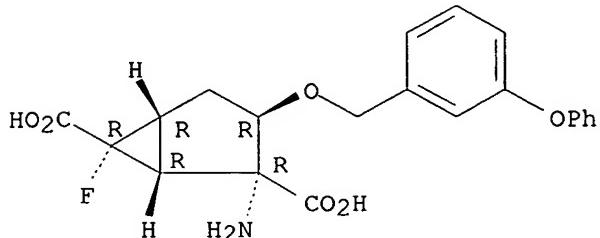
Absolute stereochemistry. Rotation (+).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-6-fluoro-3-[ (3-  
 phenoxyphenyl)methoxy]-, (1R,2R,3R,5R,6R)- (9CI)  
 MF C21 H20 F N O6

Absolute stereochemistry. Rotation (-).

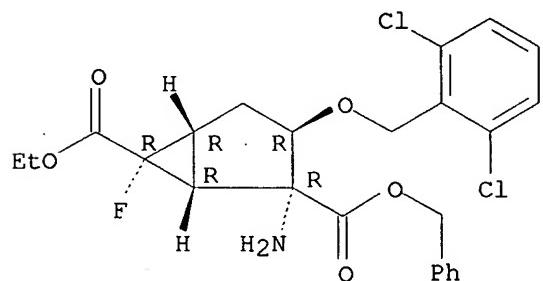


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):9

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[ (2,6-  
 dichlorophenyl)methoxy]-6-fluoro-, 6-ethyl 2-(phenylmethyl) ester,  
 (1R,2R,3R,5R,6R)- (9CI)  
 MF C24 H24 Cl2 F N O5

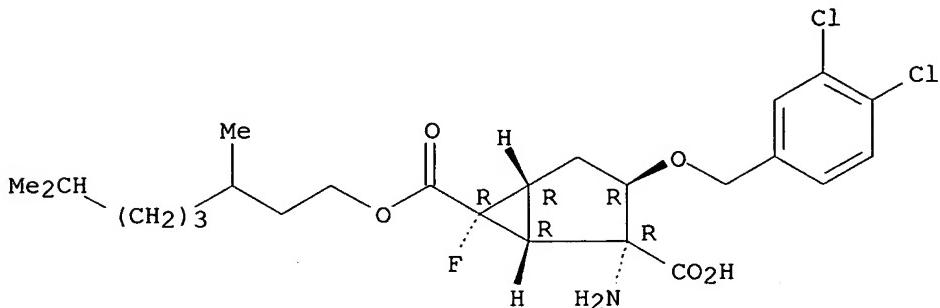
Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[(3,4-dichlorophenyl)methoxy]-6-fluoro-, 6-(3,7-dimethyloctyl) ester,  
 (1R,2R,3R,5R,6R)- (9CI)  
 MF C25 H34 Cl2 F N O5

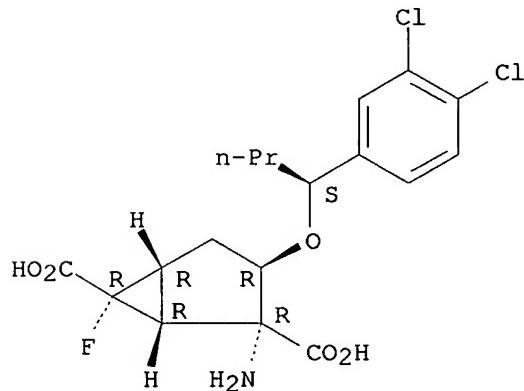
Absolute stereochemistry.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[(1S)-1-(3,4-dichlorophenyl)butoxy]-6-fluoro-, (1R,2R,3R,5R,6R)- (9CI)  
 MF C18 H20 Cl2 F N O5

Absolute stereochemistry. Rotation (+).

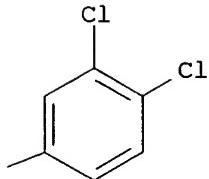
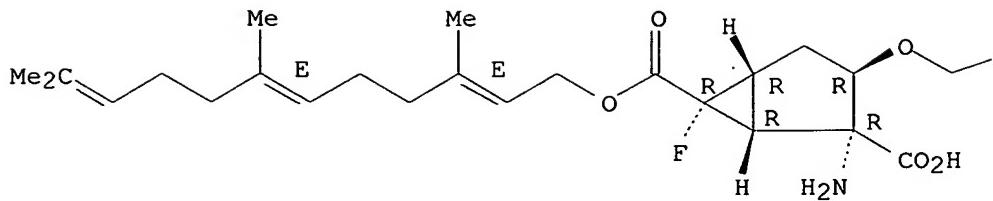


\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-3-[(3,4-dichlorophenyl)methoxy]-6-fluoro-, 6-[(2E,6E)-3,7,11-trimethyl-2,6,10-dodecatrienyl] ester, (1R,2R,3R,5R,6R)- (9CI)  
 MF C30 H38 Cl2 F N O5

Absolute stereochemistry.

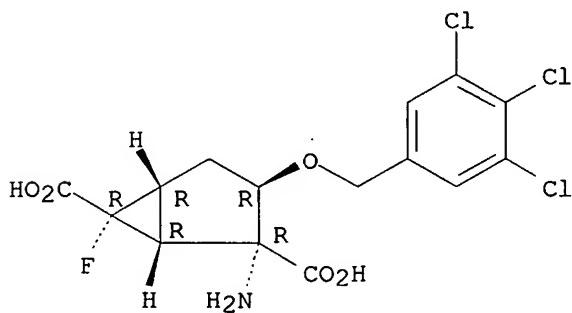
Double bond geometry as shown.



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

L2 9 ANSWERS REGISTRY COPYRIGHT 2006 ACS on STN  
 IN Bicyclo[3.1.0]hexane-2,6-dicarboxylic acid, 2-amino-6-fluoro-3-[(3,4,5-trichlorophenyl)methoxy]-, (1R,2R,3R,5R,6R)- (9CI)  
 MF C15 H13 Cl13 F N O5

Absolute stereochemistry. Rotation (-).



\*\*PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT\*\*

ALL ANSWERS HAVE BEEN SCANNED

```
=> search 11 sss full
FULL SEARCH INITIATED 13:06:18 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 273 TO ITERATE
```

100.0% PROCESSED 273 ITERATIONS
SEARCH TIME: 00.00.01

224 ANSWERS

L3 224 SEA SSS FUL L1

=> file caplus		SINCE FILE	TOTAL
COST IN U.S. DOLLARS		ENTRY	SESSION
FULL ESTIMATED COST		167.82	168.24

FILE 'CAPLUS' ENTERED AT 13:06:25 ON 05 APR 2006  
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FILE LAST UPDATED: 4 Apr 2006 (20060404/ED)

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=> 13  
L4 11 L3

=> d 14 1-11 ti

- L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell
- L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist
- L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors
- L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esters as Group II metabotropic glutamate receptor antagonists
- L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as antagonists of group II metabotropic glutamate receptor
- L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI mGluR2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivatives for treatment of nervous system diseases
- L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Anxiolytic-like activity of MGS0039, a potent group II metabotropic

glutamate receptor antagonist, in a marble-burying behavior test

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Synthesis, in vitro pharmacology, structure-activity relationships, and pharmacokinetics of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent and selective group II metabotropic glutamate receptor antagonists

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039

L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI 6-Fluorobicyclo[3.1.0]hexane derivatives

=> d 14 1-11 ti fbib abs

L4 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell  
AN 2005:1351480 CAPLUS  
DN 144:81056  
TI A metabotropic glutamate 2/3 receptor antagonist, MGS0039, increases extracellular dopamine levels in the nucleus accumbens shell  
AU Karasawa, Jun-ichi; Yoshimizu, Takao; Chaki, Shigeyuki  
CS Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Kita-ku, Saitama, 331-9530, Japan  
SO Neuroscience Letters (2006), 393(2-3), 127-130  
CODEN: NELED5; ISSN: 0304-3940  
PB Elsevier Ltd.  
DT Journal  
LA English  
AB MGS0039, a potent and selective metabotropic glutamate 2/3 (mGlu 2/3) receptor antagonist, exhibits antidepressant-like activities in some animal models. In the present study, the authors examined the effect of MGS0039 on extracellular dopamine levels in the rat nucleus accumbens (NAc) shell using in vivo microdialysis evaluation because accumbal dopamine has been implicated in depression. Local application of MGS0039 into the NAc shell at 10 µM significantly increased extracellular dopamine levels in the NAc shell in freely moving rats. In contrast, local application of 10 µM of LY354740, an mGlu 2/3 receptor agonist, significantly decreased extracellular dopamine levels in the same brain region. These findings suggest that dopamine release in the NAc shell is regulated by mGlu 2/3 receptors, and that the effect on dopamine levels in the NAc shell may partially explain the antidepressant-like properties of mGlu 2/3 receptor antagonists.

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist  
AN 2005:298938 CAPLUS  
DN 142:423678  
TI AMPA receptor stimulation mediates the antidepressant-like effect of a group II metabotropic glutamate receptor antagonist  
AU Karasawa, Jun-Ichi; Shimazaki, Toshiharu; Kawashima, Naoya; Chaki,

Shigeyuki  
CS Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, 331-9530, Japan  
SO Brain Research (2005), 1042(1), 92-98  
CODEN: BRREAP; ISSN: 0006-8993  
PB Elsevier B.V.  
DT Journal  
LA English  
AB (1R,2R,3R,5R,6R)-2-Amino-3-(3,4-dichlorobenzylxyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039), a selective group II metabotropic glutamate receptor (mGluR) antagonist, exhibits antidepressant-like activities in rodent models. In the present studies, to clarify the involvement of  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptor activation in exhibition of the antidepressant-like properties of MGS0039, the authors examined the effect of an AMPA receptor antagonist, 2,3-dihydroxy-6-nitro-7-sulfamoylbenzo(f)quinoxaline (NBQX), on the antidepressant-like effect of MGS0039 in the mouse tail suspension test. The authors also examined the effects of NBQX on increased serotonin release after treatment with MGS0039 in the rat medial prefrontal cortex (mPFC) using in vivo microdialysis evaluation. In the tail suspension test, MGS0039 (0.3-3 mg/kg, i.p.) treatment dose-dependently and significantly reduced immobility time. Pretreatment with NBQX (10 mg/kg, s.c.) significantly prevented the antidepressant-like effect of MGS0039 in the tail suspension test, while NBQX itself had no effect on immobility time. In the microdialysis evaluation, administration of MGS0039 (10 mg/kg, i.p.) significantly increased serotonin levels in mPFC in freely moving rats, while NBQX (1 mg/kg, i.p.) itself had no effect on serotonin release in this region. Pretreatment with NBQX significantly attenuated the increase in serotonin release by MGS0039. These findings suggest that stimulation of postsynaptic AMPA receptors plays a role in mediating the pharmacol. effects of MGS0039.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

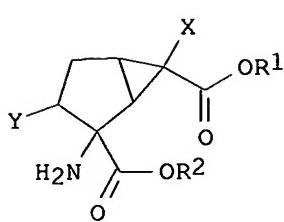
L4 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors  
AN 2005:234178 CAPLUS  
DN 142:367493  
TI Neuropharmacological profiles of antagonists of group II metabotropic glutamate receptors  
AU Kawashima, Naoya; Karasawa, Jun-ichi; Shimazaki, Toshiharu; Chaki, Shigeyuki; Okuyama, Shigeru; Yasuhara, Akito; Nakazato, Atsuro  
CS Research Strategy Group, Pharmaceutical Business Division, Taisho Pharmaceutical Co., Ltd., Saitama, Saitama, 331-9530, Japan  
SO Neuroscience Letters (2005), 378(3), 131-134  
CODEN: NELED5; ISSN: 0304-3940  
PB Elsevier Ltd.  
DT Journal  
LA English  
AB Glutamatergic abnormalities play roles in several psychiatric disorders. Glutamate acts at two classes of receptors, ionotropic and metabotropic glutamate receptors (mGluR), the latter is classified into three group, based on receptor homol. and signaling mechanisms. Among them, recent pharmacol. and histochem. studies suggest that the group II mGluR (mGluR2 and mGluR3) plays crucial roles in the control of emotional states. We previously reported that MGS0039, a selective group II mGluR antagonist, exhibited dose-dependent antidepressant-like effects in some animal models. However, the mechanism by which group II mGluR antagonists exhibit such effects is still unclear. In the present two studies, we examined neuropharmacol. effects of group II mGluR antagonists on monoaminergic neurons. In an electrophysiolog. study, MGS0039

dose-dependently and significantly increased the firing rate of dorsal raphe nucleus (DRN) serotonergic neurons. LY341495, another group II mGluR antagonist, also increased DRN serotonergic neural activity significantly. Consistent with the findings of this electrophysiol. study, MGS0039 significantly increased extracellular level of serotonin in rat medial prefrontal cortex in a microdialysis study. In contrast, MGS0039 had no effect on the activity of locus coeruleus noradrenergic neurons. These findings suggest that modulation of serotonergic neuron might be, at least in part, responsible for the antidepressant-like effects of group II mGluR antagonists.

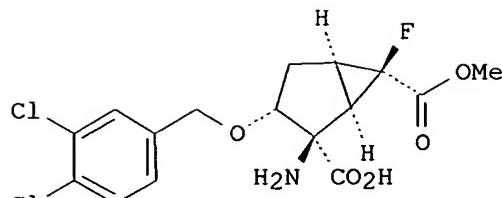
RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
 TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esters as Group II metabotropic glutamate receptor antagonists  
 AN 2005:14355 CAPLUS  
 DN 142:113634  
 TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid esters as Group II metabotropic glutamate receptor antagonists  
 IN Yasuhara, Akito; Sakagami, Kazunari; Ohta, Hiroshi; Nakazato, Atsuro  
 PA Taisho Pharmaceutical Co., Ltd., Japan  
 SO PCT Int. Appl., 144 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA Japanese  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005000791	A1	20050106	WO 2004-JP9398	20040625
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			JP 2003-181930 JP 2003-373511 JP 2004-128663	A 20030626 A 20031031 A 20040423
	AU 2004252017	A1	20050106	AU 2004-252017 JP 2003-181930 JP 2003-373511 JP 2004-128663 WO 2004-JP9398	20040625 A 20030626 A 20031031 A 20040423 W 20040625
	CA 2530706	AA	20050106	CA 2004-2530706 JP 2003-181930 JP 2003-373511 JP 2004-128663 WO 2004-JP9398	20040625 A 20030626 A 20031031 A 20040423 W 20040625
	EP 1637517	A1	20060322	EP 2004-746867 R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR	20040625 JP 2003-181930 JP 2003-373511 JP 2004-128663 WO 2004-JP9398
OS	MARPAT 142:113634	GI			A 20030626 A 20031031 A 20040423 W 20040625



I



II

AB The title compds. I [wherein R1 and R2 = independently alkyl, alkenyl, alkynyl, etc.; X = H or F; Y = (un)substituted alkoxy, SH, amino, etc.] or hydrates or pharmaceutically acceptable salts thereof are prepared as Group II metabotropic glutamate receptor antagonists. For example, the compound II was prepared in a multi-step synthesis. II showed antagonistic effect on Group II metabotropic glutamate receptor in rat. I are useful for the treatment of schizophrenia, anxiety, and diseases related to these, i.e., psychiatric disorders such as depression, bipolar disorder, and epilepsy (no data).

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as antagonists of group II metabotropic glutamate receptor  
AN 2005:14354 CAPLUS  
DN 142:113754  
TI Preparation of 2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as antagonists of group II metabotropic glutamate receptor  
IN Yasuhara, Akito; Sakagami, Kazunari; Ohta, Hiroshi; Nakazato, Atsuro  
PA Taisho Pharmaceutical Co., Ltd., Japan  
SO PCT Int. Appl., 86 pp.  
CODEN: PIXXD2

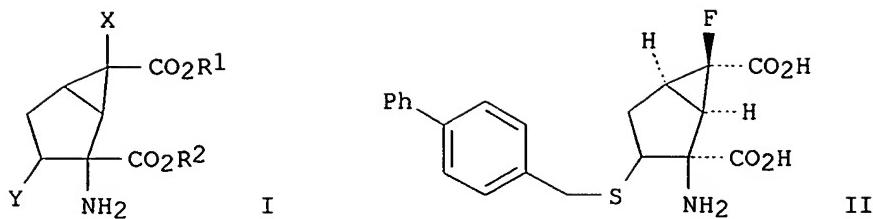
DT Patent

LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2005000790	A1	20050106	WO 2004-JP9384	20040625
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
				JP 2003-181931	A 20030626

OS MARPAT 142:113754  
GI



AB The title compds. [I; R1, R2 = H, C1-10 alkyl, Ph, naphthyl, mono- or diphenyl-C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, hydroxy-C2-10 alkyl, C1-10 alkoxy carbonyl-C1-10 alkyl, amino-C2-10 alkyl, C1-10 alkoxy-C1-10 alkyl; X = H, F; Y = NH<sub>2</sub>, SR<sub>3</sub>, S(O)nR<sub>7</sub>, SCHR<sub>3</sub>R<sub>4</sub>, S(O)nCHR<sub>3</sub>R<sub>4</sub>, N(CHR<sub>3</sub>R<sub>4</sub>)(CHR<sub>5</sub>R<sub>6</sub>), NHCOR<sub>3</sub>, O<sub>2</sub>CR<sub>7</sub>; wherein R<sub>3</sub>-R<sub>6</sub> = H, C1-10 alkyl, (un)substituted Ph, naphthyl, 1-7 halogen(s)-substituted naphthyl, heteroaryl; R<sub>7</sub> = C1-10 alkyl, (un)substituted Ph, naphthyl, 1-7 halogen(s)-substituted naphthyl, heteroaryl; n = 1,2], pharmaceutically acceptable salts thereof, or hydrates of either are prepared. These compds., e.g. (II), had an antagonistic effect on a Group II metabotropic glutamate receptor with IC<sub>50</sub> of ≤200 nM, and are effective in treatments for and prevention of psychiatric disorders and neurol. diseases.

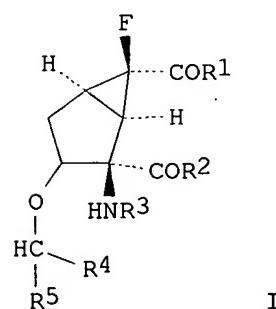
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI mGluR2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivatives for treatment of nervous system diseases  
AN 2004:1038326 CAPLUS  
DN 142:16843  
TI mGluR2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivatives for treatment of nervous system diseases  
IN Nakazato, Atsuro; Taki, Shigeyuki; Sakagami, Kazunari; Dean, Reiko; Ota, Hiroyuki; Hirota, Shiho; Yasuhara, Akitaka  
PA Taisho Pharmaceutical Co., Ltd., Japan  
SO Jpn. Kokai Tokkyo Koho, 70 pp.  
CODEN: JKXXAF

DT Patent  
LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	JP 2004339199	A2	20041202	JP 2004-86153 JP 2003-117907	20040324 A 20030423
OS	MARPAT 142:16843				



AB The antidepressant mGlur2 antagonists and 2-amino-3-alkoxy-6-[3.1.0]hexan-2,6-dicarboxylate derivs., salts, and hydrates are claimed for treatment of nervous system diseases, including bipolar affective disorder, psychiatry disorder, anxiety, epilepsy, drug dependence, cognition disorder, Alzheimer's disease, Huntington's disease, Parkinson disease, muscle stiffness, brain ischemia, spinal cord injury, head injury, etc.

L4 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

TI Anxiolytic-like activity of MGS0039, a potent group II metabotropic glutamate receptor antagonist, in a marble-burying behavior test

AN 2004:814656 CAPLUS

DN 141:325597

TI Anxiolytic-like activity of MGS0039, a potent group II metabotropic glutamate receptor antagonist, in a marble-burying behavior test

AU Shimazaki, Toshiharu; Iijima, Michihiko; Chaki, Shigeyuki

CS Psychiatric Diseases and Pain Research, Medicinal Pharmacology Laboratory, Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Saitama, 331-9530, Japan

SO European Journal of Pharmacology (2004), 501(1-3), 121-125

CODEN: EJPHAZ; ISSN: 0014-2999

PB Elsevier B.V.

DT Journal

LA English

AB Glutamatergic abnormalities are involved in several psychiatric disorders. Clin. evidence demonstrates altered glutamatergic neurotransmission in patients suffering from obsessive-compulsive disorder. MGS0039, (1R,2R,3R,5R,6R)-2-amino-3-(3,4-dichlorobenzyloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid, is a novel group II metabotropic glutamate (mGlu) receptor antagonist. We examined MGS0039's potential anti-obsessive-compulsive disorder activity, using the marble-burying behavior test as a model of obsessive-compulsive disorder. MGS0039 as well as LY341495 ((2S,1'S,2'S)-2-(9-xanthylmethyl)-2-(2'-carboxycycloprolyl)glycine), another group II mGlu receptor antagonist, inhibited marble-burying behavior. We also demonstrated that this effect was significantly attenuated by a group II mGlu receptor agonist. This data indicates that group II mGlu receptor antagonists may exert anti-obsessive-compulsive disorder effects in clin. use.

RE.CNT 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

TI Synthesis, in vitro pharmacology, structure-activity relationships, and pharmacokinetics of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent and selective group II metabotropic glutamate receptor antagonists

AN 2004:620394 CAPLUS

DN 141:243074

TI Synthesis, in vitro pharmacology, structure-activity relationships, and pharmacokinetics of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivatives as potent and selective group II metabotropic glutamate receptor antagonists

AU Nakazato, Atsuro; Sakagami, Kazunari; Yasuhara, Akito; Ohta, Hiroshi; Yoshikawa, Ryoko; Itoh, Manabu; Nakamura, Masato; Chaki, Shigeyuki

CS Medicinal Chemistry Laboratory, Taisho Pharmaceutical Co. Ltd., Kita-ku, Saitama-shi, Saitama, 331-9530, Japan

SO Journal of Medicinal Chemistry (2004), 47(18), 4570-4587

CODEN: JMCMAR; ISSN: 0022-2623

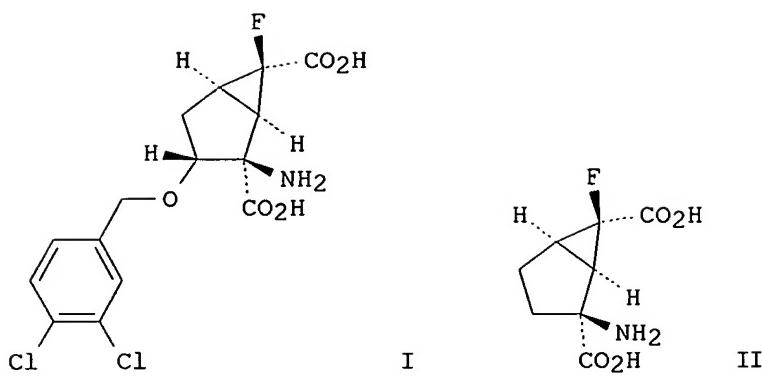
PB American Chemical Society

DT Journal

LA English

OS CASREACT 141:243074

GI



**AB** Group II metabotropic glutamate receptor (mGluR) antagonists, 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs., e.g., I, were discovered by the incorporation of a hydroxy or alkoxy group onto the C-3 portion of selective and potent group II mGluR agonist II. Among these compds., I (MGS0039) was a highly selective and potent group II mGluR antagonist with the best pharmacokinetic profile. I exhibited high affinities for mGlu 2 ( $K_i = 2.38 \pm 0.40$  nM) and mGlu 3 ( $4.46 \pm 0.31$  nM) but low affinity for mGluR 7 ( $K_i = 664 \pm 106$  nM), and potent antagonist activities for mGlu 2 ( $IC_{50} = 20.0 \pm 3.67$  nM) and mGluR 3 ( $IC_{50} = 24.0 \pm 3.54$  nM) but much less potent antagonist activities for mGlu 4 ( $IC_{50} = 1740 \pm 1080$  nM), mGlu 6 ( $IC_{50} = 2060 \pm 1270$  nM), mGlu 1 ( $IC_{50} = 93300 \pm 14600$  nM), and mGluR 5 ( $IC_{50} = 117000 \pm 38600$  nM). No significant agonist activities of I were found for mGluRs 2, 3, 4, 6, 1, and 5 ( $EC_{50} > 100000$  nM). Furthermore, I exhibited dose-dependent oral absorption (plasma  $C_{max} = 214 \pm 56.7$ ,  $932 \pm 235$ , and  $2960 \pm 1150$  ng/mL for 3 mg/kg, 10 mg/kg, and 30 mg/kg, po, resp.) and acceptable blood-brain barrier penetration (brain  $C_{max} = 13.2$  ng/mL for 10 mg/kg, po 6 h). The synthesis, in vitro pharmacol. profile, and structure-activity relationships of 3-alkoxy-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid derivs., and pharmacokinetic profiles of several typical compds, are presented.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
 TI MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity  
 AN 2004:126085 CAPLUS  
 DN 141:82129  
 TI MGS0039: a potent and selective group II metabotropic glutamate receptor antagonist with antidepressant-like activity  
 AU Chaki, Shigeyuki; Yoshikawa, Ryoko; Hirota, Shiho; Shimazaki, Toshiharu; Maeda, Maoko; Kawashima, Naoya; Yoshimizu, Takao; Yasuhara, Akito; Sakagami, Kazunari; Okuyama, Shigeru; Nakanishi, Shigetada; Nakazato, Atsuro  
 CS Medicinal Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, 331-9530, Japan  
 SO Neuropharmacology (2004), 46(4), 457-467  
 CODEN: NEPHBW; ISSN: 0028-3908  
 PB Elsevier Science B.V.  
 DT Journal  
 LA English  
 AB The present study describes the pharmacol. profile of (1R,2R,3R,5R,6R)-2-

Amino-3-(3,4-dichlorobenzylloxy)-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039), a novel group II mGluR antagonist. MGS0039 showed high affinity for both mGluR2 ( $K_i = 2.2$  nM) and mGluR3 ( $K_i = 4.5$  nM), which are comparable to LY341495, another group II mGluR antagonist. MGS0039 attenuated both glutamate-induced inhibition of forskolin-evoked cAMP formation in CHO cells expressing mGluR2 ( $IC_{50} = 20$  nM) or mGluR3 ( $IC_{50}=24$  nM) and glutamate-increased [ $^{35}S$ ]GTP $\gamma$ S binding to mGluR2 ( $pA_2=8.2$ ), which means that MGS0039 acts as an antagonist. MGS0039 shifted the dose-response curve of glutamate-increased [ $^{35}S$ ]GTP $\gamma$ S binding rightward without altering the maximal response, and thereby indicating competitive antagonism. MGS0039 showed no significant effects on other mGluRs as well as the other receptors and transporters we studied. MGS0039 (0.3-3 mg/kg, i.p.) as well as LY341495 (0.1-3 mg/kg, i.p.) had dose-dependent antidepressant-like effects in the rat forced swim test and in the mouse tail suspension test. In contrast, MGS0039 (0.3-3 mg/kg, i.p.) had no apparent effect in the rat social interaction test and in the rat elevated plus-maze. These results indicate that MGS0039 is a potent and selective antagonist of group II mGluR, and that group II mGluR antagonists, like MGS0039, have an antidepressant-like potential in exptl. animal models.

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN  
TI Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039  
AN 2004:96754 CAPLUS  
DN 140:368470  
TI Increased cell proliferation in the adult mouse hippocampus following chronic administration of group II metabotropic glutamate receptor antagonist, MGS0039  
AU Yoshimizu, Takao; Chaki, Shigeyuki  
CS Medicinal Research Laboratories, Medicinal Pharmacology Laboratory, Psychiatric Diseases and Pain Research, Taisho Pharmaceutical Co., Ltd., Kita-ku, Saitama, 331-9530, Japan  
SO Biochemical and Biophysical Research Communications (2004), 315(2), 493-496  
CODEN: BBRCA9; ISSN: 0006-291X  
PB Elsevier Science  
DT Journal  
LA English  
AB We have previously reported that MGS0039, a novel antagonist of group II metabotropic glutamate receptors (mGluRs), exerts antidepressant-like effects in exptl. animal models. Recent studies suggest that the behavioral effects of chronic antidepressant treatment are mediated by the stimulation of neurogenesis in the hippocampus. In the present study, we examined the effects of MGS0039 on cell proliferation in the adult mouse hippocampus. MGS0039 (5 or 10 mg/kg) or fluvoxamine was administered chronically to male ICR mice over a period of 14 days. Multiple bromodeoxyuridine (BrdU) administrations were performed after the last drug injection to label dividing cells. Immunohistochem. analyses after BrdU injections revealed that chronic MGS0039 treatment enhanced BrdU-pos. cells in the dentate gyrus (.apprx.62% increase) in the same manner as chronic fluvoxamine treatment. This is the first in vivo study to demonstrate an increase in cell proliferation following a blockade of group II mGluRs. These findings raise the possibility that MGS0039 may exert antidepressant-like effects by modulating cell proliferation in the hippocampus.

RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

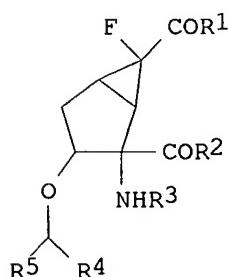
L4 ANSWER 11 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

TI 6-Fluorobicyclo[3.1.0]hexane derivatives  
 AN 2003:591035 CAPLUS  
 DN 139:143973  
 TI 6-Fluorobicyclo[3.1.0]hexane derivatives  
 IN Nakazato, Atsuro; Chaki, Shigeyuki; Sakagami, Kazunari; Dean, Ryoko; Ohta, Hiroshi; Hirota, Shiho; Yasuhara, Akito  
 PA Taisho Pharmaceutical Co.,ltd., Japan  
 SO PCT Int. Appl., 98 pp.  
 CODEN: PIXXD2

DT Patent  
 LA Japanese  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2003061698	A1	20030731	WO 2002-JP13693	20021226
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			JP 2001-395797	A 20011227
	CA 2471642	AA	20030731	CA 2002-2471642	20021226
				JP 2001-395797	A 20011227
				WO 2002-JP13693	W 20021226
EP	1459765	A1	20040922	EP 2002-793421	20021226
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK			JP 2001-395797	A 20011227
				WO 2002-JP13693	W 20021226
BR	2002015462	A	20041130	BR 2002-15462	20021226
				JP 2001-395797	A 20011227
				WO 2002-JP13693	W 20021226
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				JP 2001-395797	A 20011227
				WO 2002-JP13693	W 20021226
ZA	2005002085	A	20050629	ZA 2005-2085	20021226
				JP 2001-395797	A 20011227
ZA	2004004795	A	20050617	ZA 2004-4795	20040617
				JP 2001-395797	A 20011227

OS MARPAT 139:143973  
 GI



AB Antidepressants containing as the active ingredient compds. having group II metabotropic glutamate receptor antagonism; and 2-amino-3-alkoxy-6-fluorobicyclo[3.1.0]- hexane-2,6-dicarboxylic acid derivs. represented by the general formula [I], pharmaceutically acceptable salts thereof, or hydrates of the salts: I wherein R1 and R2 may be the same or different from each other and are each hydroxyl, C1-10 alkoxy, or the like; R3 is C1-10 acyl, C1-6 alkoxy-C1-6 acyl, or the like; and R4 and R5 may be the same or different from each other and are each hydrogen, C1-10 alkyl, or the like.

RE.CNT 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

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COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION

FULL ESTIMATED COST

35.15 203.39

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION

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STN INTERNATIONAL SESSION SUSPENDED AT 13:08:29 ON 05 APR 2006